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H. pylori infection, atrophic gastritis, cytokines, gastrin, COX-2, PPARγ and impaired apoptosis in gastric carcinogenesis

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Summary

Background: *Helicobacter pylori* (Hp) infection represents a crucial factor in pathogenesis of gastric cancer (GC). Factors emanating from *bacterium* as well as from environmental contributions such as salt diet and inadequate supply of antioxidants, affect the risk for GC development.

Results: Atrophic gastritis is considered to be a precursor lesion of intestinal type GC that is accompanied by hypergastrinemia with subsequent induction of cyclooxygenase-2 (COX-2), whose products are responsible for slowing apoptosis and for angiogenesis in GC tumor. The involvement of proinflammatory cytokines (especially IL-1 and IL-8) and reactive oxygen species (ROS) due to NFκB activation, increased cell proliferation combined with inhibition of apoptosis as well as upregulation of peroxisome proliferation activated receptor gamma (PPARγ) and inducible nitric oxide synthase (iNOS) appear to be major molecular biology alterations in pathogenesis of GC.

Conclusions: These results suggest the therapeutic usefulness of inhibitors of gastrin expression and release such as powerful somatostatin analogs (Sandostatin) or blockers of COX-2 (coxibs) in the control of GC development and progression as chemopreventive agents. Comparative genomic and proteomic is the key in identifying biomarkers in host and *bacterium* for the prediction of gastric cancer in Hp-infected patients.

key words: **gastric cancer • *Helicobacter pylori* • gastrin • cytokines • Coxibs • somatostatin • peroxisome proliferator-activated receptor gamma**

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HELICOBACTER PYLORI INFECTION AND CORREA CASCADE IN DEVELOPMENT OF GASTRIC CANCER

Helicobacter pylori (Hp) is the major environmental contributory factor in the development of gastric cancer (GC) which still remains a major health problem worldwide. Almost 10 years ago, Hp was classified by the World Health Organization (WHO) as a group 1 carcinogen [1]. Support for this view has been mainly provided by epidemiological studies. A number of studies including our own showed that the prevalence of Hp and CagA in GC patients is much higher than in age- and gender-matched controls [2,3] (Figures 1 and 2). Individuals with previous Hp infection have significantly increased risk of GC (4 to 6 folds) [4,5] and the risk of development of GC is clearly related to the CagA expression of Hp and the duration of Hp infection accounting in part for the increasing rates of GC in older individuals [3,6]. There is also significant geographic relation between GC mortality rates and the Hp prevalence [7]. Countries with increased Hp prevalence exhibit also higher rates of GC and the decline in the GC involving antrum during last century (see Figure 1) concerns predominantly those parts of the world in which the rate of Hp prevalence is also declining (Figure 3). The only exception, that seems to confirms the above-mentioned rule, is Africa, where despite high Hp prevalence, the rate of GC remains low, so called 'African Enigma'. The high parasite infestation and ingestion of plant food with higher content of antioxidants in this part of the world may somehow protect the stomach from development of GC. Also in our country, in the region of the highest (almost 100%) Hp infection rate, among Tatra Mountain shepherds and their families [8], the rate of GC appears quite low. This phenomenon could, however, be explained by the overuse of certain alcoholic beverages, especially red vines ('*Grzaniec góralski*' – hot punch) with spices, possessing anti-Hp effects due to their phenolic compounds [9] exhibiting antioxidant, cancer suppressing and stimulating effect on the synthesis of nitric oxide, which has been shown to protect the mucosa against damage and to stimulate the mucosal repair and healing of mucosal inflammation, erosions and ulcerations [10].

On the other hand, despite an assumption that Hp infection plays a crucial role in the pathogenesis of GC, only a small proportion (1–2%) of infected patients develop GC (see Figure 3). Thus, the Hp infection may be neither essential nor wholly responsible for the process of malignant transformation. In fact, the majority of Hp infected patients does not develop GC, while a number of Hp-seronegative patients do develop GC (up to 20%). Therefore, in addition to Hp other environmental and host factors must be important [11]. According to our experience following the occurrence of gastric atrophy, usually the Hp detection becomes difficult despite of the obvious premalignant changes in the gastric mucosa. Simply the Hp disappears from the stomach with marked atrophic changes perhaps due to lack of nutrients for this germ. In addition, as shown recently by Semino-Mora et al. [12], bacteria may hide themselves within the mucosal cells without causing alterations in

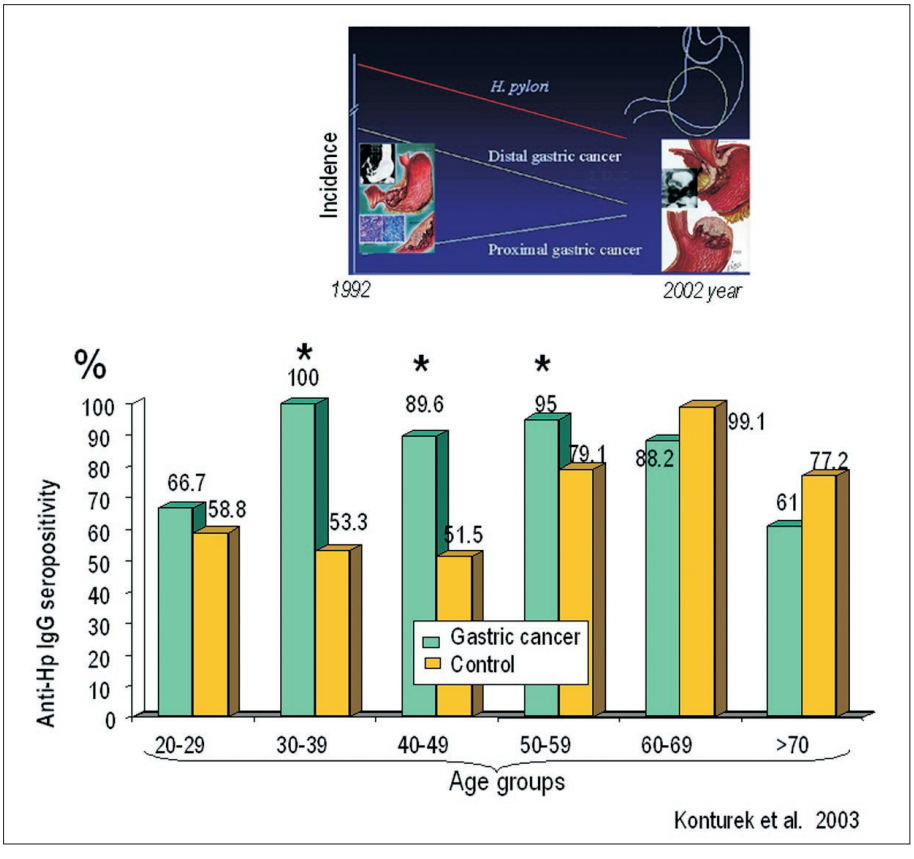

Figure 1.
Anti-Hp IgG seropositivity in GC patients and age- and gender-matched controls in various age groups. According to our observations, there is a tendency of Hp infection to decline during last decade combined with the fall in the occurrence of GC at the distal part of the stomach, while at the same time there is an increase of GC at the proximal portion of the stomach.

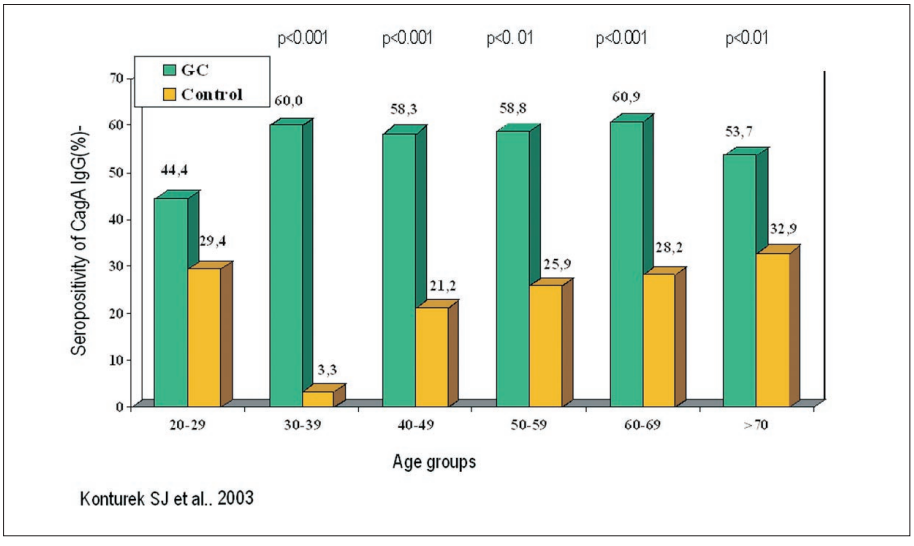

Figure 2.
CagA Hp IgG seropositivity in GC patients and age- and gender-matched controls in the various age groups.

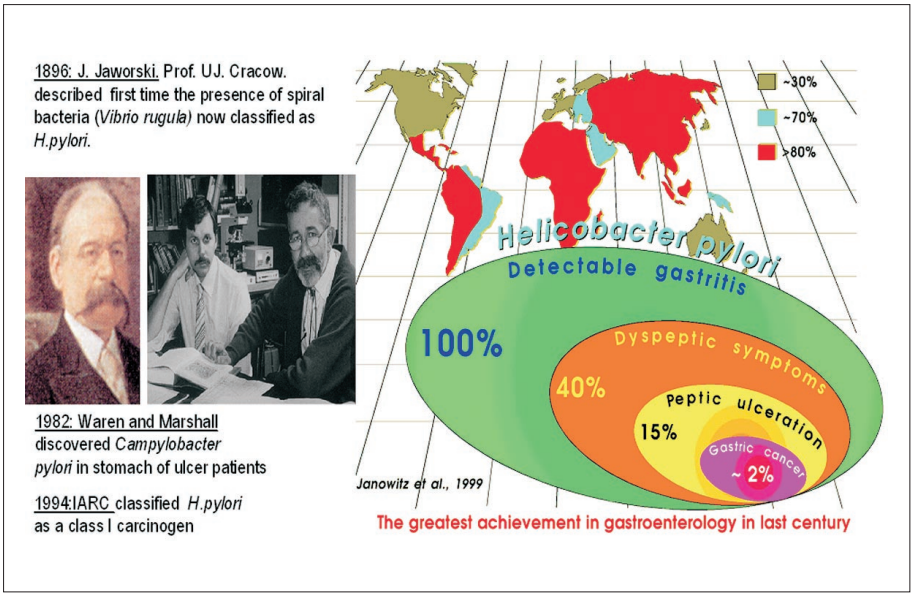

Figure 3.
Hp prevalence in populations in various parts of the world and related consequences of Hp infection including GC (on the right). Discoverers of Hp in humans [13,14] (on left).

immunological system (Hp serology negative) and without producing urease in the gastric lumen so that the urea breath test detecting active Hp infection becomes negative.

There is little doubt that, at least one type of tumor, gastric lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is causally related to Hp infection as it is acquired in gastric mucosa almost in 100% in association with Hp infection. Clinical studies have shown that the eradication of *bacterium*, at least from early lesions, results in tumor regression in 60 to 92% [14,15] (Figure 4)

From pathological point of view, the development of intestinal-type GC involves progression through a well-defined series of histological steps, initiated by the change of normal mucosa to chronic superficial gastritis, followed by the appearance of atrophic gastritis and intestinal metaplasia, then dysplasia and finally adenocarcinoma preceded and accompanied by numerous changes in molecular biology of mucosa cells, particularly in the regeneration zone of gastric glands from which all types of GC originate (Figure 5). These subsequent pathological changes from gastritis to gastric dysplasia and GC was recognized by Correa [2] long before the Hp was discovered as major gastric pathogen by Marshall and Warren [13,14] and this sequence is called 'Correa's cascade'. Following discovery of Hp, Correa included this pathogen in his cascade and ascribed to it the major role in GC pathogenesis (Figure 5 and 6).

It is now clear that patients with pangastritis are prone to the development of gastric atrophy and progression to GC. In contrast, gastritis predeminantly located in *antrum* (*antrum*-predominant gastritis) that is associated with hypergastrinemia and hyperchlorhydria may result in duodenal ulcerations that somehow 'protect' the stomach from development of GC (Figure 7). In con-

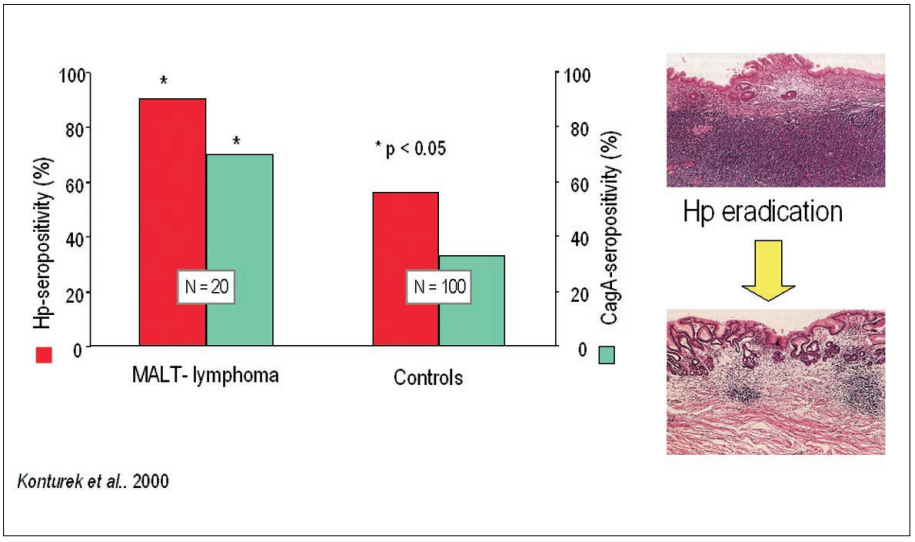

Figure 4.
Prevalence of Hp and CagA seropositivity in low-grade gastric MALT-lymphoma (on left) and the regression of MALT tumor following eradication of Hp (on right).

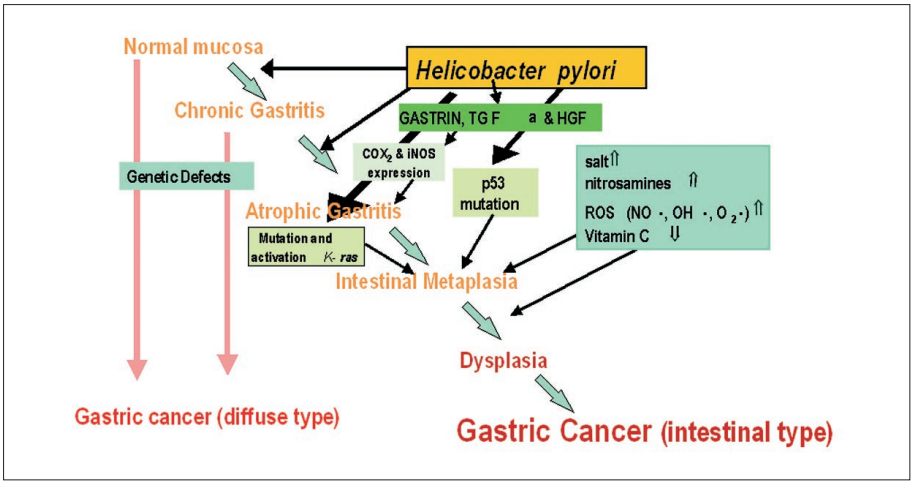

Figure 5.
Molecular basis of gastric cancerogenesis.

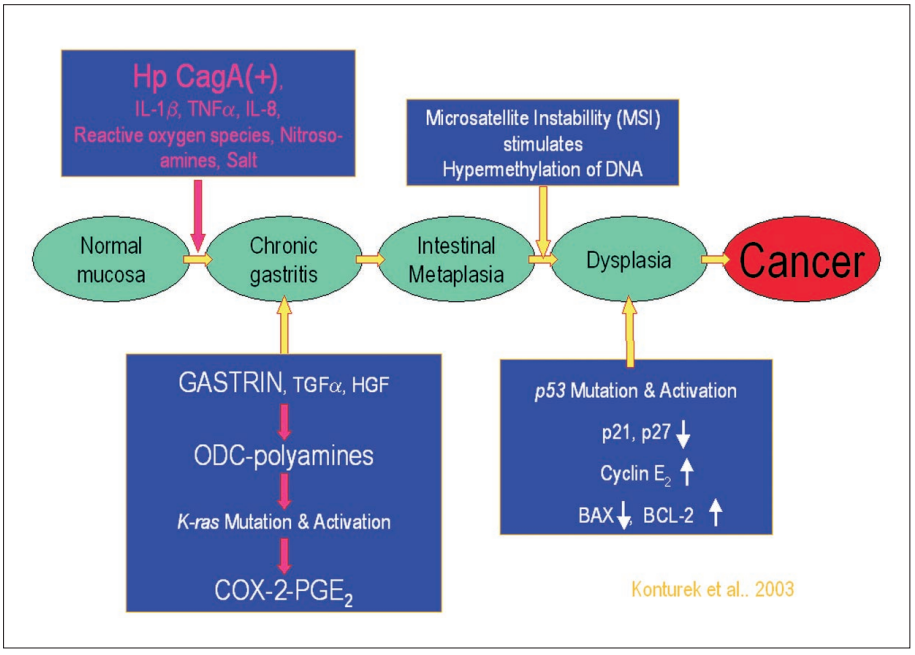

Figure 6.
Modified Correa's cascade with inclusion of Hp infection in gastric cancerogenesis.

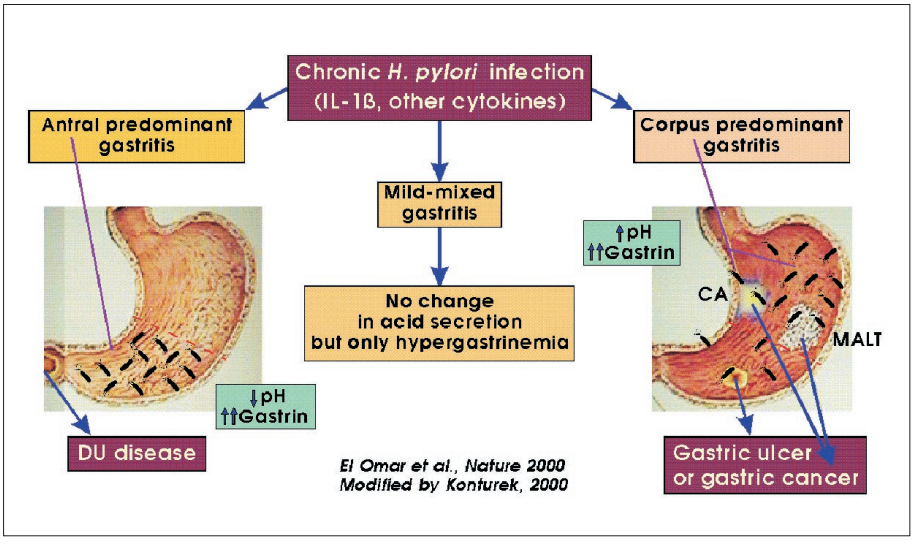

Figure 7.
Ulcerogenic or cancerogenic action of Hp infection depends upon the localization of the infection. *Antrum*-predominant gastritis leads to duodenal ulcer *via* increased gastrin release and gastric acid hypersecretion, while *corpus*-predominant gastritis results in gastric atrophy with gastric ulcer, MALT lymphoma or GC.

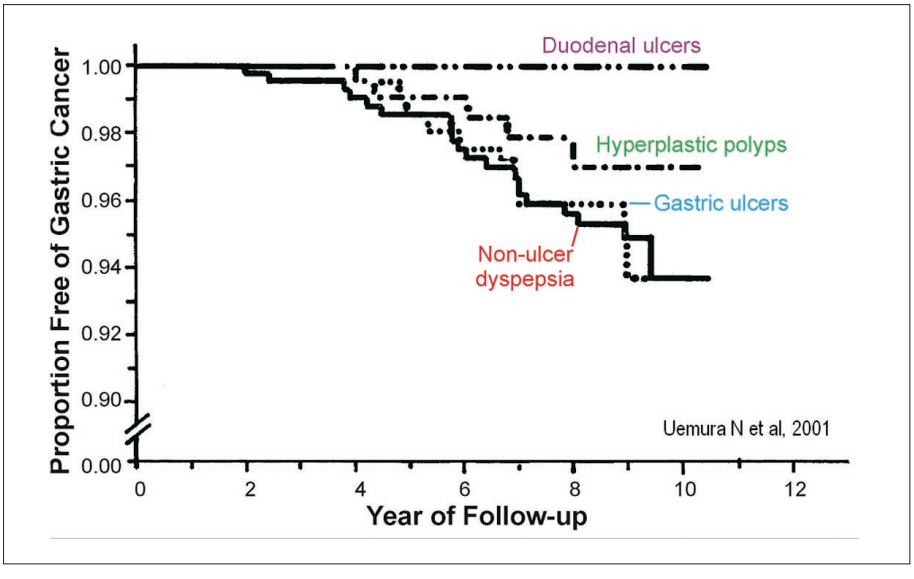

Figure 8.
Results of prospective studies of Uemura et al. [16] on effects of prolong Hp infection on development of GC in patients with duodenal ulcerations, hyperplastic polyps, gastric ulcers or non-ulcer dyspepsia.

trast, '*corpus*-predominant gastritis', though similarly accompanied by hypergastrinemia due to decrease of gastric acid and the removal of acid-controlled suppression of antral somatostatin, tends to progress into metaplasia, atrophy, dysplasia and GC [14,15]. The strongest evidence for the association between Hp infection and GC development was provided by the prospective study of Uemura et al. [16] (Figure 8). In this study a large number of patients with Hp infection were followed with serial endoscopic examinations. Over time, GC was not diagnosed in Hp negative patients or in patients who had duodenal ulcer. In contrast, the risk for GC was highly increased in Hp positive patients with gastric ulcers, hyperplastic polyps and non-ulcer dyspepsia. Uemura and Okamoto [17] revealed that in patients with early GC subjected to endoscopic mucosal resection but without Hp therapy, new GC was found in 13% as opposed to only 1% on GC relapse during 4–7 years in similar group of patients subjected to GC mucosectomy combined with eradication of Hp. The difference in GC occurrence between eradication group (N=65) and non-treated group (N=67) was highly significant. It is of interest that such eradication in early GC group was followed by the improvement of gastric acid secretion, remission of *corpus*-gastritis and decrease of nitroso compounds associated with gastric carcinogenesis. These studies indicate that Hp positive GC patients should be eradicated even before the surgery to reduce the progression of ongoing gastric carcinogenesis.

MICROBIAL AND HOST FACTORS IN CANCER DEVELOPMENT

It appears that increased risk for the development of GC in Hp infected patients depends on both microbial and host factors (Figure 9). Among microbial factors, especially the gene expression for Cag pathogenicity island (PAI) (a large region of the genome containing approximately 30 genes), is an important determinant of GC development in Hp infected patients. Some of the genes of the Cag PAI have close similarities to a type IV

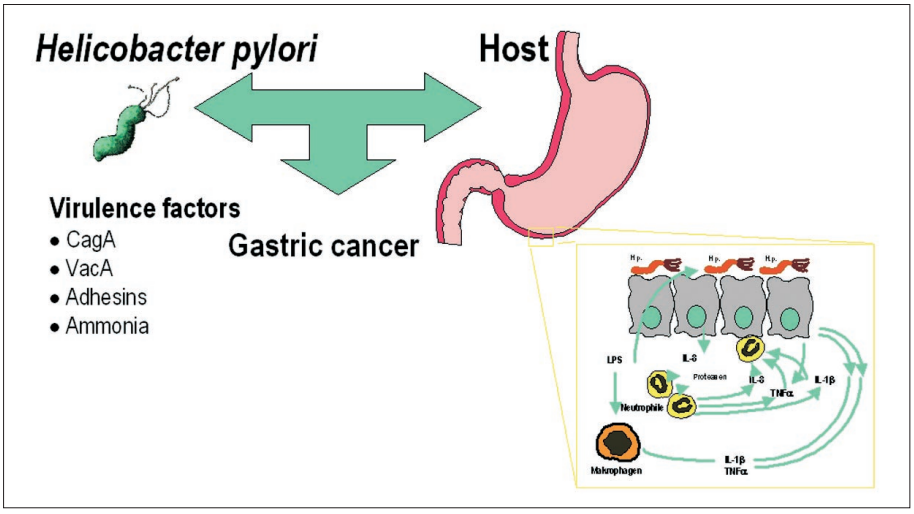

Figure 9.
Mucosal lesions depends upon the virulence of Hp and immunological conditions of host.

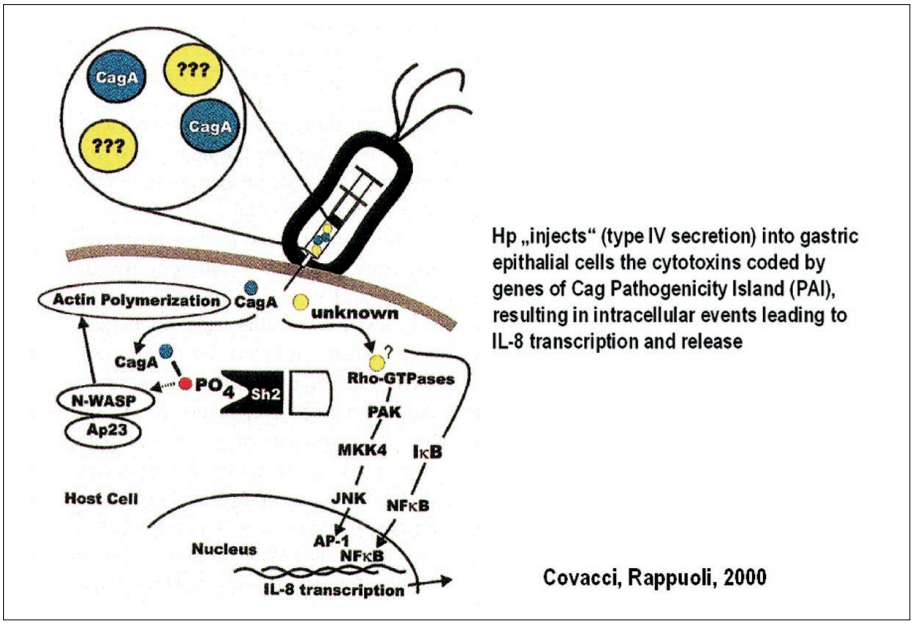

Figure 10.
Genes of Cag pathogenicity island encodes type IV secretion system which provides the mechanism for direct transfer of bacterial effector protein (cytotoxins) into eucaryotic host mucosal cell (Covacci and Rappuoli, 2000).

secretion system [18]. This system provides the mechanisms for a direct transfer of bacterial cytotoxic protein into eucaryotic host cells. The CagA was shown to be translocated from adherent bacterial cell to epithelial cell. This leads to phosphorylation of CagA on the tyrosine residue by cellular kinases. This induces cell morphological changes including actin polymerization and pedestal formation, possible by activating N-WASP. It may also trigger a signaling cascade *via* MAP pathway, which may induce the transcription of nuclear genes [19] (Figure 10). It is postulated that CagA by still not completely unclair mechanisms activates NFκB signaling system leading to the increased production of cytokines such as IL-8. It is possible that increased IL-8 may result in a greater degree of gastritis, ultimately predisposing to the development of GC [20,21], but exact mechanism involved in CagA-IL-8 promotion of cancerogenesis remains to be elucidated, but there is little doubt that CagA positive Hp infection remarkably raises the risk of GC (see Figure 2). Another important virulence factor is a vacuolating cytotoxin (VacA) [22]. A *vacA* gene is present in virtually all of the Hp strains examined. However, strains vary considerably in the production of vacuolating cytotoxin. This is attributed to the variation in *vacA* gene structure. Also factors responsible for the attachment of Hp to gastric epithelium (blood group antigen binding adhesin BabA encoded by *babA* or sialic acid binding adhesin) are important microbial factors associated with an increased risk for GC development [21,22].

Concerning the host answer, a multiple pathways are involved in the gastric carcinogenesis including chronic inflammatory response with predominant lymphocyte Th1 answer, increased cell proliferation due to activation of protooncogenes, increased expression of mucosal growth factors and hypergastrinaemia with overexpression of COX-2. Finally, polymorphisms of host

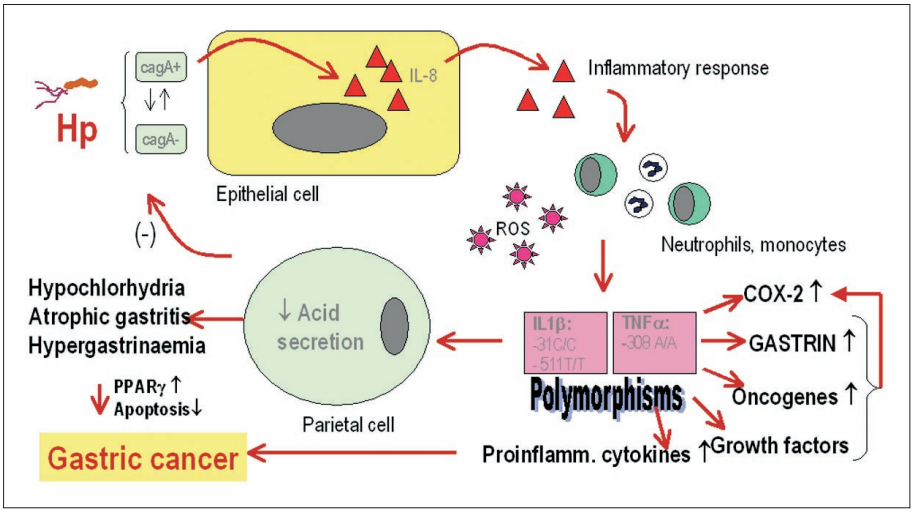

Figure 11.
Development of GC depends upon the interaction of microbial and host factors.

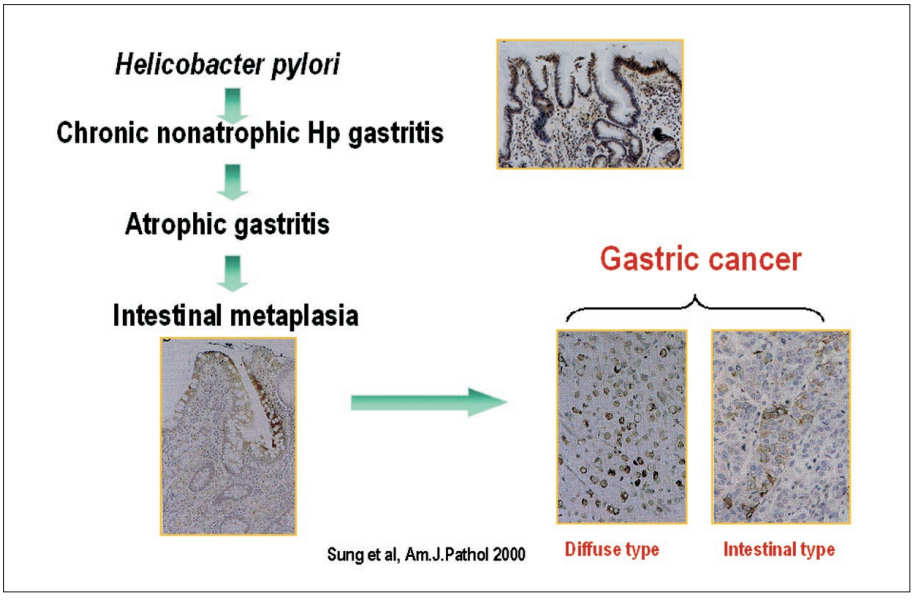

Figure 12.
COX-2 immunostaining in Hp-induced atrophic gastritis, intestinal metaplasia and GC tissue of intestinal or diffuse type.

genes for inflammatory cytokines such as IL-1β and TNFα [23] and excessive production of prostaglandins (PG) and upregulation of PPARγ (with subsequent alteration in apoptosis lead to GC development (Figure 11)

COX-2 EXPRESSION IN DEVELOPMENT OF GASTRIC CANCER AND THERAPEUTICAL PROPOSAL

The increased expression of mitogenic metabolites of arachidonic acid such as PG due to COX-2 overexpression in gastric mucosa during Hp infection could represent an important link between Hp-induced gastritis and gastric carcinogenesis (Figure 12). Our previous studies demonstrated a significant upregulation of COX-2 expression at the mRNA and protein level in Hp infected gastric mucosa [23]. The procarcinogenic actions of COX-2-derived PG stimulated by Hp (Figure 13) include the stimulation of cell proliferation, the inhibition of apoptosis, the induction of angiogenesis and the direct mutagenic effect [25] (Figure 14).

The involvement of COX-2 overexpression in gastric carcinogenesis suggests that COX-2 blockade might be useful in chemoprevention against gastric cancer. Our recent human study performed in GC patients showed that 14-day treatment with selective COX-2 blocker resulted in a significant decrease in plasma and tumor contents of both amidated gastrins and their precursor, progastrin [25]. This treatment led also to significant upregulation of caspase-3 mediating apoptotic cell death [25,26]. Our recent studies suggest that application of somatostatin and its powerful analog such as Sandostatin Lar (Novartis, Pharma), suppresses the COX-2 expression and reduces the generation of gastrin by cancer cells, thus slowing down the tumor growth and metastatses [26] (Figure 15). This therapeutical approach may not only be applicable to hypergastrinemic cancers such as gastrinoma but also to ordinary GC expressing progastrin and its products, amidated gastrins, the most potent inducers of COX-2 in GC tumor and surrounding gastric mucosa infected with Hp.

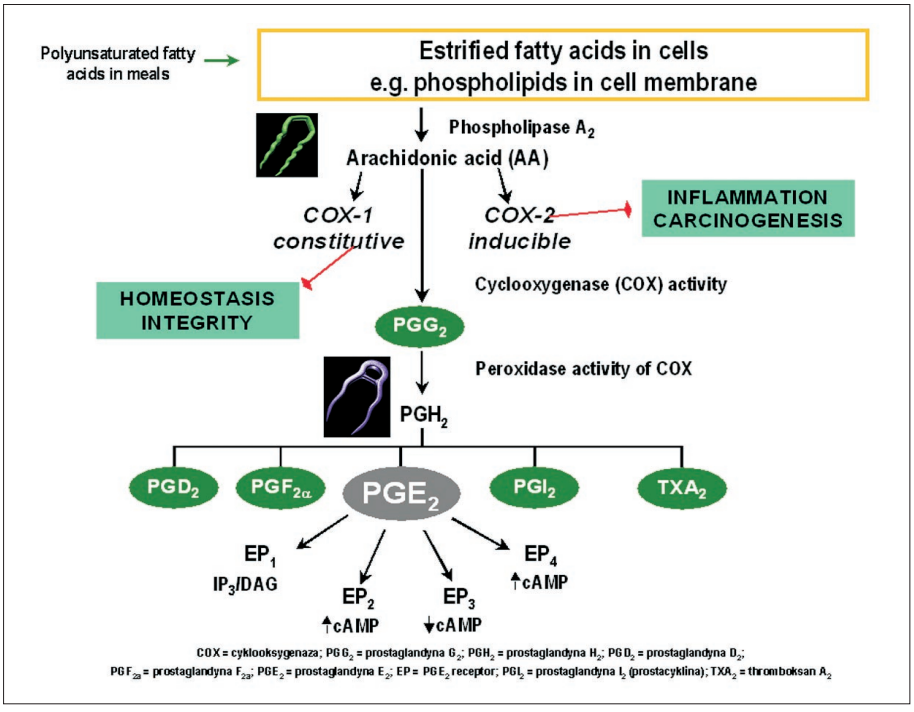

Figure 13.
Arachidonic acid metabolism and its products through the action of COX-1 and COX-2.

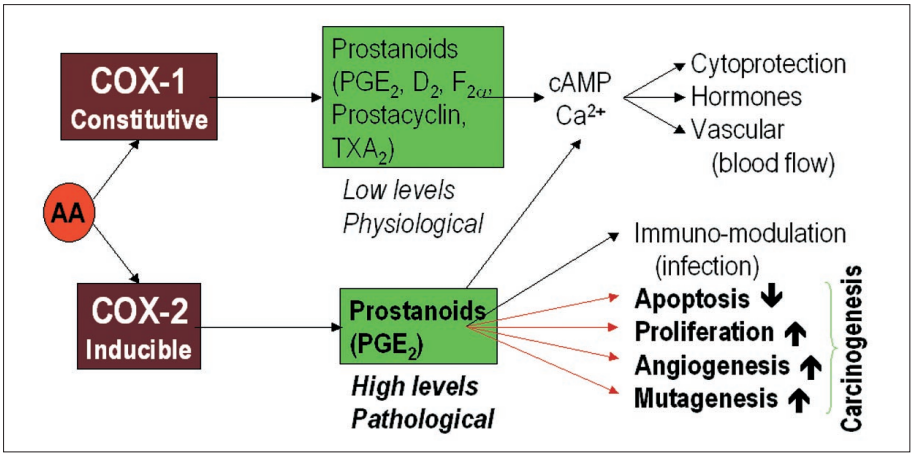

Figure 14.
Biological action of COX-1 and COX-2 metabolites.

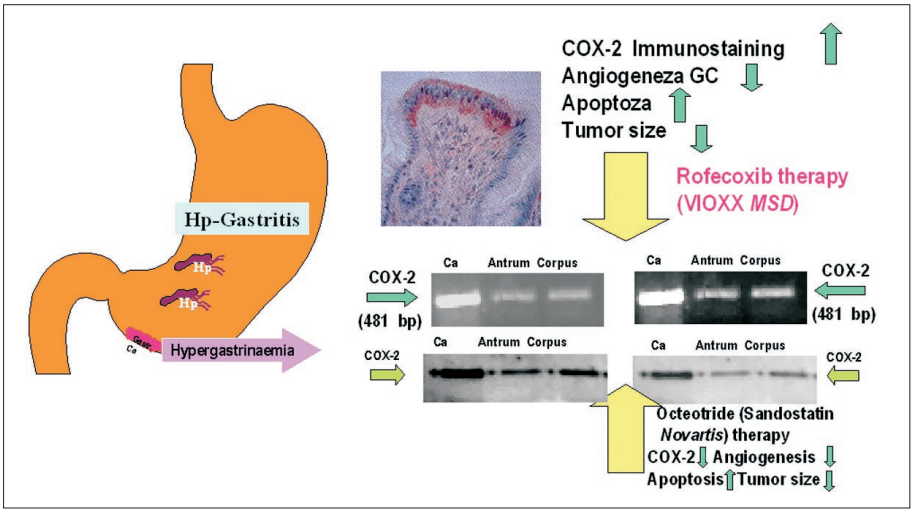

Figure 15.
Inhibition of COX-2 I by Rofecoxib (Vioxx) leads to upregulation of COX-2 and induction of apoptosis in GC, while reducing the tumor size and angiogenesis. Administration of Sandostatin Lar (Novartis) results in the attenuation of COX-2 expression and the fall in gastrin production by GC tumor.

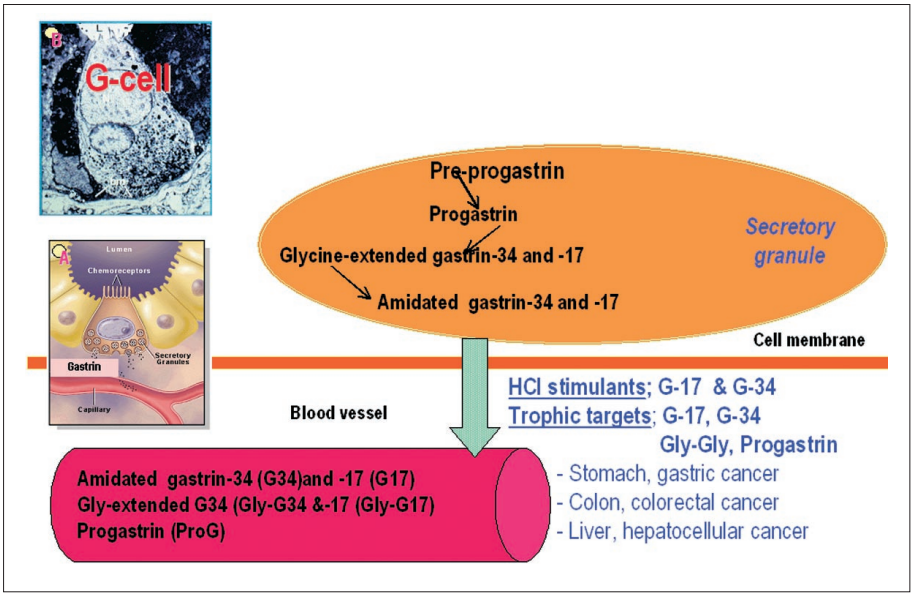

Figure 16.
Production of gastrin in G-cells of antral mucosa and the precursors of gastrin; pre-progastrin and progastrin and Gly-Gly-extended gastrin. The latters are Involved in gastric and colorectal carcinogenesis.

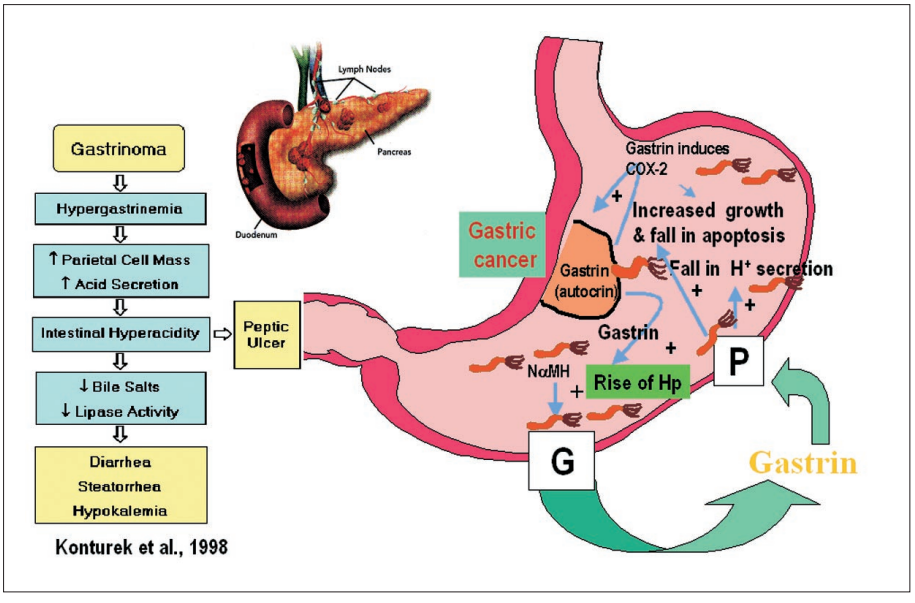

Figure 17.
Hypergastrinemia and duodenal ulcers in gastrinoma patients (on left) and role of gastrin and COX-2 in Hp-induced gastric carcinogenesis (on right).

Among the growth factors, gastrin appears to be one of the most important gastrointestinal hormones involved in the physiological stimulation of cell proliferation at regeneration zone of glands in the oxyntic and colon mucosa and in tumor tissue (Figure 16). Hp infection in gastric mucosa is associated with increased plasma gastrin release, originating from the action on G-cells or cancer cells of N-α methyl-histamine (NαMH) released by Hp, a potent gastrin-releasing substance in Hp-infected stomach (Figure 17). Also proinflammatory cytokines are known to stimulate gastrin expression and release in GC (Figure 18). The previous studies have shown that gastrin after binding to its receptor (CCK_B-R) activates the cascade of phosphorylation reaction which targets ERKs (Extracellular Signal-Regulated Kinases) *via* both protein kinase C-dependent and C–independent pathways. The ERKs in turn appear to activate early response of genes such as *c-fos* or *c-jun* which appears to be essential for activation of cell proliferation [27–29].

In our earlier studies we demonstrated in GC significantly increased gastrin levels in serum, gastric juice and GC tissues. We demonstrated for the first time the presence of gastrin immunoreactivity and gastrin immunostaining in GC biopsy samples [30–32]. More importantly, the gene expression for gastrin receptor (CCK_B-R) was detected in GC tissue (Figure 19). This indicates that gastrin produced in excessive amounts in GC tumor stimulates the tumor growth by autoregulative mechanism [32]. In addition, Hp infection may result in the upregulation of gene expression of certain growth factors such as EGF or HGF, that were found to decline following the eradication of Hp [31,32].

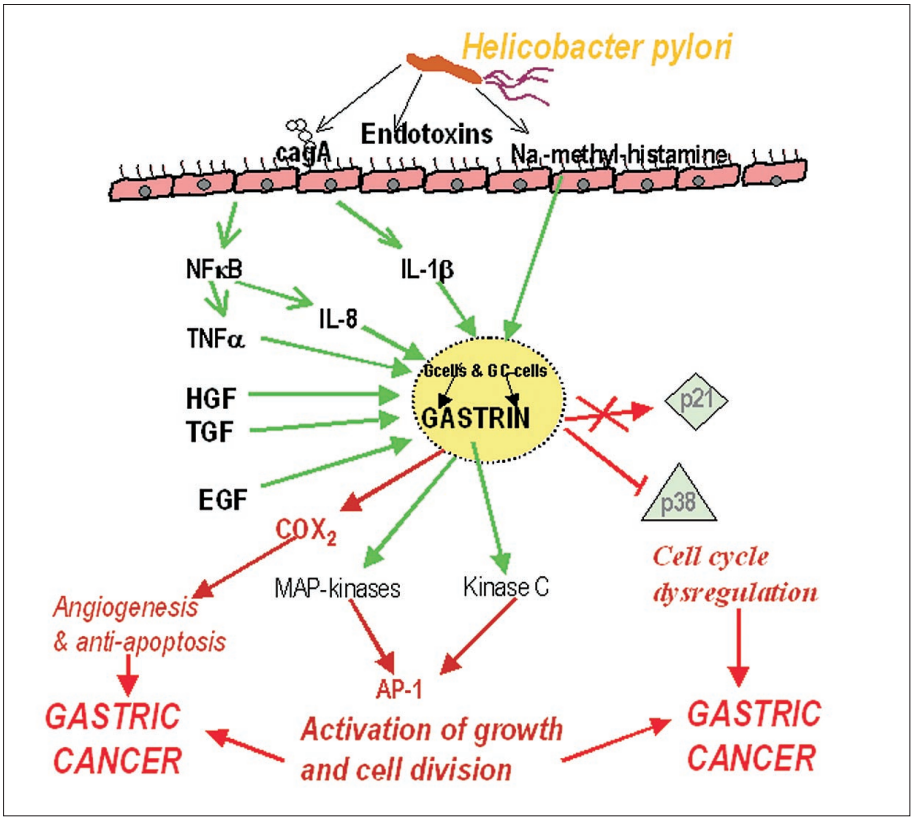

Figure 18.
Crucial role of gastrin in gastric carcinogenesis *via* direct stimulation of the proliferation of cancer cells, COX-2 induction with subsequent angiogenesis, anti-apoptosis and cell cycle dysregulation.

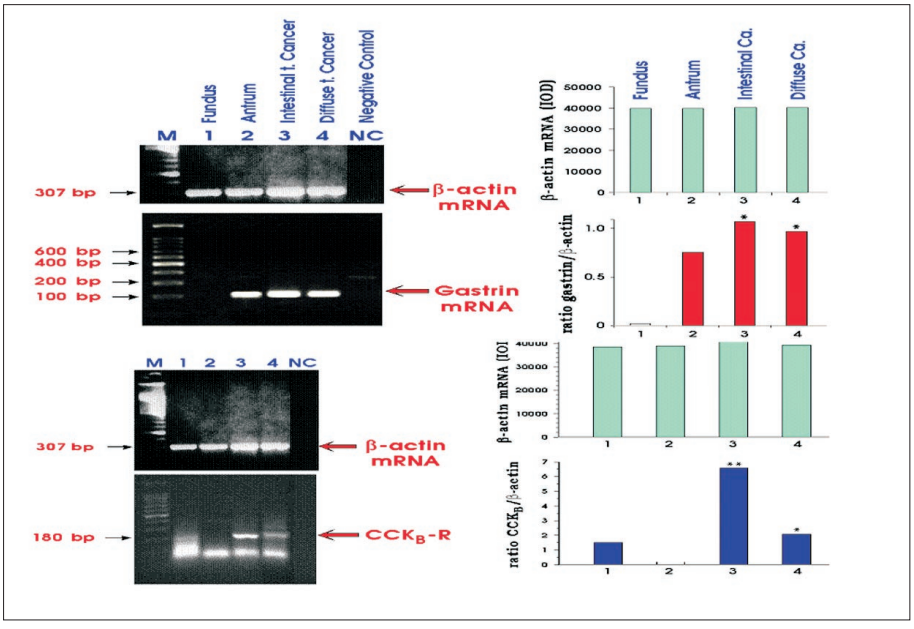

Figure 19.
Gene expression of gastrin and its receptors (CCK_B-R) in gastric *antrum* and *corpus* as well as in the intestinal and diffuse types GC cells.

The precise mechanism by which gastrin promotes gastric carcinogenesis remains still unclear. Our recent *in vitro* study using gastric cancer cell line confirmed that gastrin stimulates strongly the expression of HGF, an important mucosal growth factors, and COX-2 that inhibits cell apoptosis [32]. Furthermore, we found that exogenous gastrin has a stimulatory effect on the expression of antiapoptotic BCl-2 and survivin, which play a critical role in the regulation of apoptosis as important antiapoptotic proteins [32]. These data indicate that gastrin has stimulatory effect on cancer cell proliferation and concurrently shows antiapoptotic activities (Figure 20). These results suggest that the reduction in gastrin gene expression and subsequent suppression of its enhancing action on COX-2 expression, using inhibitor of gastrin release such as powerful

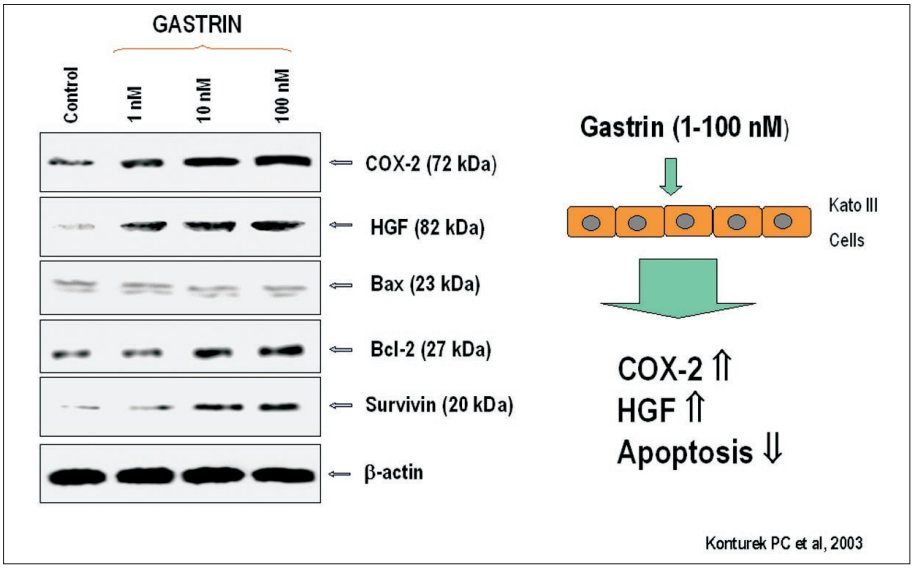

Figure 20.
Effect of increasing concentrations of gastrin (G-17) on gene expresson of COX-2, HGF, and apoptosis regulating proteins (Bax, Bcl-2, Survivin) in isolated gastric cancer cells [30].

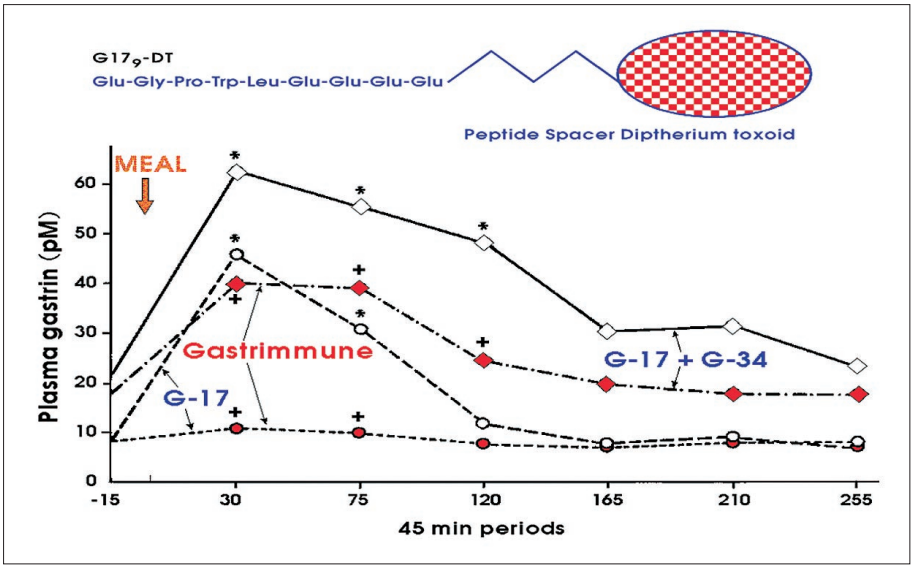

Figure 21.
The influence of 'vaccination' with complex of G-17 + *Diphterium* toxoid 'Gastrimmune' on plasma levels of gastrin-17 (G-17) and combination of G-17 + G-34 of 10 patients with advanced colorectal cancer and hypergastrinemia before and after meat-meal feeding (unpublished data).

somatostatin analog (octeotride) combined with the attenuation of expression of COX-2 by specific blockers 'coxibs' may be fully justified as another therapeutical approach in the control of progression of GC. Attempts to immunoneutralize gastrins produced by gastric or colorectal cancer using 'vaccination' with G-17 complexed with *Diphterium* toxin resulted in only small increase of the survival of patients with advanced GC or colorectal cancers [33]. We found that failure could be due to the immunoneutralization of only one species of gastrin, namely G-17, while others including G-34 and progastrin (involved in stimulation of cancer cell growth) remained unaffected (Figure 21). Further attempts to use similar 'gastrimmune' but directed against major types of gastrin species overproduced in GC or colorectal cancer may provide new tool for suppressing gastrins playing crucial role in cancerogenesis in the stomach and colon.

PPARs AND CANCER GROWTH – POSSIBLE THERAPEUTIC IMPLICATIONS

The peroxisome proliferator-activated receptors (PPARs) represent a family of nuclear receptors that are closely related to thyroid hormone or retinoid receptors. Three PPAR subtypes (PPARα, PPARδ, PPARγ) have been identified so far [34]. However, PPARγ is the most extensively studied of the three PPAR subtypes to date. Upon ligand binding, PPAR activates the transcription of many PPAR responsive genes involved in the regulation of adipocyte differentiation, the enhancement of target tissues to insulin, the inflammation, the carcinogenesis and the cell cycle control [35] (Figure 22). Recently, the increase in PPARγ expression parallel to COX-2 overexpression was found in the gastric mucosa of Mongolian gerbils infected with Hp which is accepted as the best animal model for Hp-induced gastric carcinogenesis [35] (Figure 22). In addition to these data, Takahashi et al. [36] observed

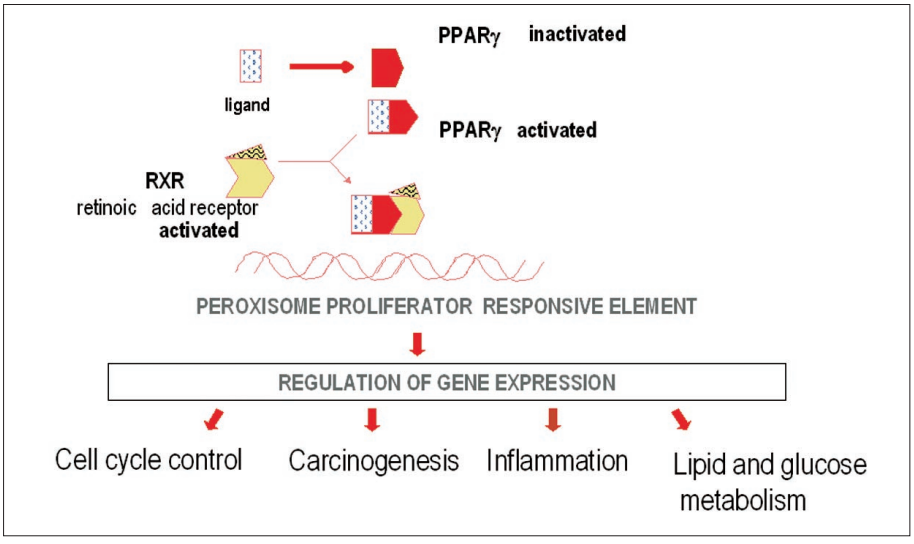

Figure 22.
Activation of PPAR(by specific ligands results in alteration of gene expression of substances involved in cell cycle control, carcinogenesis, inflammation and lipid-glucose metabolism.

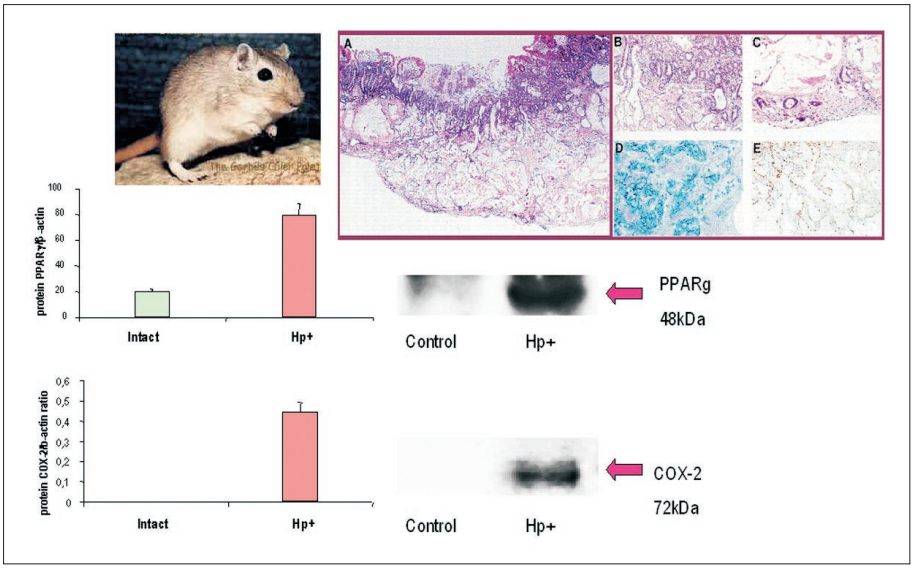

Figure 23.
Role of nitric oxide in gastric carcinogenesis. Expression of iNOS mRNA in the gastric cancer tissue (line 2) and non-tumorous adjacent gastric mucosa (line 1) and non-infected normal gastric mucosa (line 3).

a pronounced inhibition of cell growth and induction of apoptosis in human gastric cancer cells. These data indicates that the PPARγ ligands may have potential as chemotherapeutic agents for treatment of GC but this option has not been explored [36].

Induction of nitric oxide synthase (iNOS) and gastric cancer (GC)

Current information suggests that nitric oxide (NO) may contribute to carcinogenesis representing an important link between chronic inflammation and gastric carcinogenesis. The postulated role of NO in carcinogenesis involves modulation of transcription factors (NFκB, AP-1 pathways etc), direct oxidative DNA damage, stimulation of angiogenesis, inhibition of DNA repair enzymes, dysregulation of apoptosis and activation of oncogene expression [37]. The recent paper by Touati et al. [38] demonstrated a direct gastric mutagenic effect due to Hp infection in the Big Blue transgenic mouse model. This effect was associated with a 5-fold increase in the expression of iNOS [37,38]. In accordance to these data we found recently a significant elevation of iNOS expression in the biopsy taken from gastric cancer as compared to non-cancerous gastric mucosa (Figure 24).

Conclusions

In conclusion, Hp infection represents one of the major gastric carcinogens. Factors emanating from host, *bacterium* and other environmental factors influence the risk for GC development in atrophic gastric mucosa. The molecular mechanisms of gastric carcinogenesis are complex and involve increased production of proinflammatory cytokines and reactive oxygen species due to NFκB activation, increased cell proliferation and inhibition of apoptosis caused by hypergastrinaemia and activation of protooncogenes, alterations in epithelial cell growth due to overexpression of gastrin and its receptors, COX-2, PPARγ and iNOS. Each of these factors involved in gastric

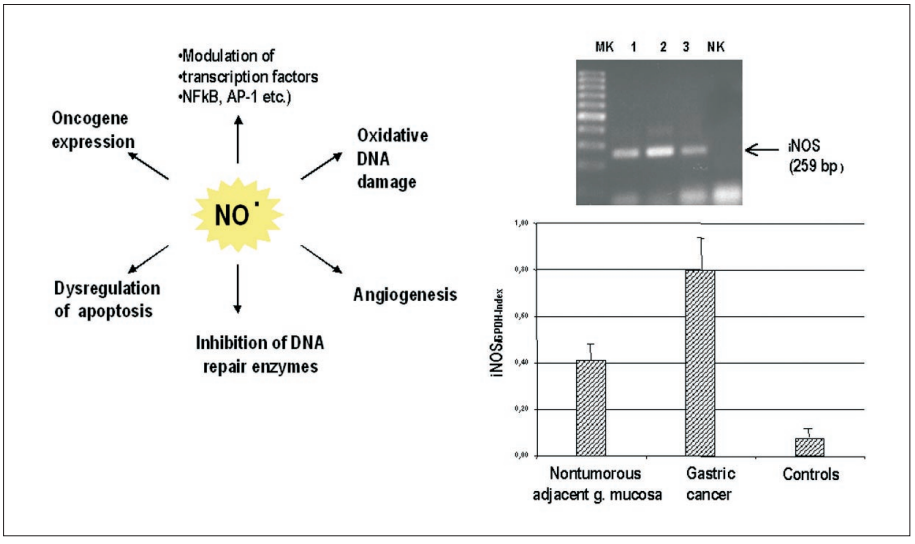

Figure 24.
Hp infection of stomach in Mongolian gerbils stimulates the expression of PPARγ and COX-2, resulting in the development of GC in these animals.

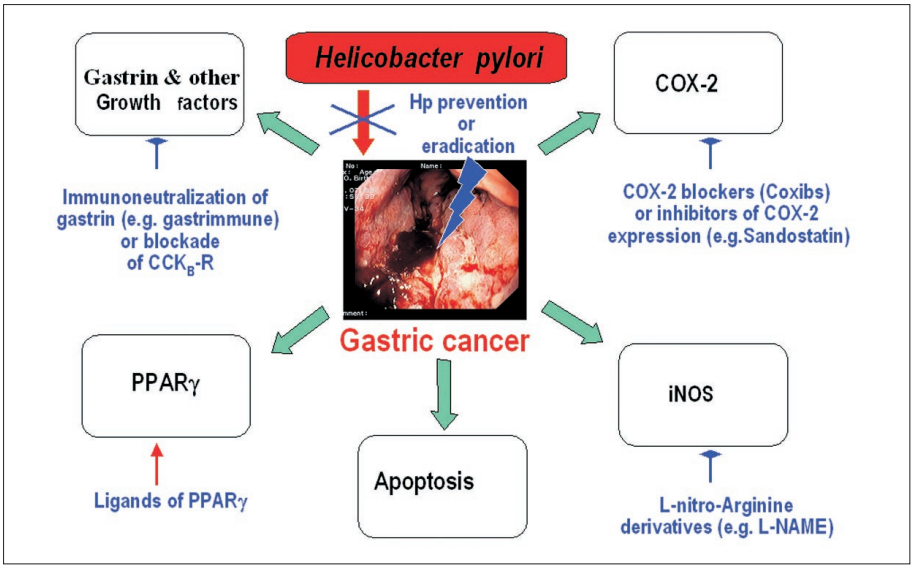

Figure 25.
Possible targets for chemoprevention of GC.

ulcerogenesis may serve as cancer biomarkers and represent potential target of chemoprevention (Figure 25).

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